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An Evaluation of the Markers p53 and Ki-67 for Their Predictive Value in Prostate Cancer

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Background and Objectives: p53 and Ki-67 are but two markers being evaluated for their predictive value in prostate cancer. The purpose of this study was to compare p53 and Ki-67 with age, stage, Gleason score, and ploidy for their prognostic abilities in prostate cancer.

Methods: Prostate cancer specimens from 134 patients were immunohistochemically stained for p53 and Ki-67 expression and differences evaluated by SPSS analysis of variance (ANOVA) methods. The dependent variable was patient survival and the independent variables were age, stage, Gleason score, and ploidy.

Results: In decreasing order of prediction of survival were stage ($P < 0.001$), Gleason score ($P < 0.001$), age ($P = 0.1869$), Ki-67 ($P = 0.2284$), p53 ($P = 0.4282$) and ploidy ($P = 0.8141$).

Conclusion: It is concluded that stage and Gleason score are significant predictors of survival while p53, Ki-67, age and ploidy are not.

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KEY WORDS: **prostate cancer; p53; Ki-67; prognostic indicator; predictive value**

INTRODUCTION

Prostate cancer is first in incidence and second in mortality of males in the United States [1]. Survival varies according to the biologic potential of the tumor. Determinants of the biologic potential of the tumor have traditionally been age, stage and type of therapy. More recently molecular biology has provided newer markers of biologic potential [2–5]. Two of these markers are p53 and Ki-67. The purpose of this study was to evaluate the predictive value of p53 and Ki-67 in prostate cancer specimens from 172 patients with a diagnosis of prostate cancer.

MATERIALS

There were 172 patients with a histologic diagnosis of prostate cancer evaluated. Data for all parameters was not available for all patients, hence some totals are for lesser numbers.

Age. There were 92 patients less than 70 years of age and 76 patients 70 years or older (Table I).

Stage. There were 69 patients with stage A disease, 38 with stage B, 24 with stage C, and 40 with stage D, respectively.

Gleason score. There were 31 patients with Gleason scores of 2–4, 106 with scores 5–7 and 29 with scores 8–10, respectively.

Ploidy. There were 77 patients with diploid tumors and 82 with nondiploid tumors.

Markers. A total of 134 patients were evaluated for expression of p53 and 121 patients were evaluated for Ki-67 proliferation indices.

METHODS

p53 expression was determined immunohistochemically employing the Dako (Carpinteria, CA) monoclonal

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TABLE I. Patient Survival (in Months) for Evaluated Population Variables

Variable	Patients (%)	Survival ± SE	95% Conf. limits
Age			
<70	92 (54.8)	86.2 ± 5.5	(76–97)
⩾70	76 (45.2)	72.1 ± 6.9	(59–86)
	168		
Stage			
A	69 (40.4)	91.6 ± 6.1	(80–104)
B	38 (22.2)	84.1 ± 9.0	(67–102)
C	24 (14.0)	78.8 ± 8.6	(62–96)
D	40 (23.4)	47.5 ± 6.8	(34–61)
	171		
Gleason score			
Grades 2–4	31 (18.7)	101.2 ± 9.0	(84–119)
Grades 5–7	106 (63.9)	83.2 ± 5.3	(73–94)
Grades 8–10	29 (17.5)	43.7 ± 7.5	(29–58)
	166		
Ploidy			
Diploid	77 (48.4)	88.5 ± 5.9	(77–100)
Nondiploid	82 (51.6)	73.6 ± 6.6	(61–87)
	159		
Markers			
p53 expressed			
Yes	33 (24.6)	72.4 ± 8.1	(56–88)
No	101 (75.4)	83.7 ± 5.7	(72–95)
	134		
Ki-67 expressed			
Yes	59 (48.8)	73.9 ± 7.0	(60–88)
No	62 (51.2)	88.2 ± 6.9	(75–102)
	121		

antibody. Ki-67 proliferation was determined immunohistochemically employing the Coulter (Hialeah, FL) monoclonal antibody. Patient survivals were Kaplan-Meier observed survivals. Statistics were preformed using analysis of variance (ANOVA) programs of the SPSS software package, licensed through Rush Presbyterian–St. Lukes Medical Center, Chicago. A value of $P < 0.05$ is considered significant. Differences within various parameters was evaluated by Chi-square analysis and two-tailed analysis was used for generation of *P*-values.

RESULTS

The survivals (in months) by variables are summarized in Table I.

p53

Survivals (in months) for p53 expression by variables are expressed in Table II. Those not expressing p53 had significantly ($P < 0.05$) diminished survival with Gleason grades 8–10 (40.2 ± 7.8; 95% confidence limits [CL] 25–56%) compared to those not expressing p53 with Gleason grades 2–4 (89.9 ± 12.8; 95% CL 65–115%) or Gleason grades 5–7 (90.0 ± 7.4; 95% CL 75–105%). In those not expressing p53 and having stage D disease, there was also significantly ($P < 0.05$) diminished survival (50.5 ± 8.6; 95% CL 34–67%) compared to those not expressing p53 with stage A disease (87.1 ± 8.4; 95% CL 71–104%). Age did not produce significant differences, although the greatest survival was found in those

TABLE II. Patient Survival (in Months) by p53 Expression and by Evaluated Patient Variables

		p53 positive			p53 negative		
Marker	Total no. of patients	N	Survival mean ± SE[a]	95% Conf. limits	N	Survival mean ± SE[a]	95% Conf. limits
p53	134	33	72.4 ± 8.1	(56–88)	101	83.7 ± 5.1	(73–95)
Age <70	74	19	68.4 ± 8.5	(52–85)	55	93.8 ± 7.4	(79–108)
Age ⩾70	57	12	81.4 ± 15.9	(50–113)	45	64.6 ± 7.7	(49–80)
	131	31			100		
Stage A	51	11	82.5 ± 12.3	(58–107)	40	87.1 ± 8.4	(71–104)
Stage B	27	7	74.7 ± 22.3	(31–119)	20	73.4 ± 5.6	(62–84)
Stage C	18	4	80.3 ± 16.7	(48–113)	14	77.2 ± 7.6	(62–92)
Stage D	38	11	40.8 ± 7.1	(27–55)	27	50.5 ± 8.6	(34–67)
	134	33			101		Stage D vs. A*
Gleason 2–4	22	3	83.0 ± 38.1	(8–158)	19	89.9 ± 12.8	(65–115)
Gleason 5–7	84	23	78.8 ± 9.7	(60–98)	61	90.0 ± 7.4	(75–105)
Gleason 8–10	26	7	49.1 ± 16.1	(18–81)	19	40.2 ± 7.8	(25–56)
	132	33			99		Gleason 8–10* vs. 2–4 and 5–7
Diploid	62	18	81.1 ± 11.2	(59–103)	44	87.8 ± 8.1	(72–104)
Nondiploid	65	14	54.4 ± 9.6	(36–73)	51	81.4 ± 8.6	(65–98)
	127	32			95		

[a]SE, standard error.
*Significant, at $P < 0.05$.

TABLE III. Patient Survival (in Months) by Ki-67 Expression and by Evaluated Patient Variables

		Ki-67 positive			Ki-67 negative		
Marker	Total no. of patients	N	Survival mean ± SE[a]	95% Conf. limits	N	Survival mean ± SE[a]	95% Conf. limits
Ki-67	121	59	73.9 ± 7.0	(60–88)	62	88.2 ± 6.9	(75–102)
Age <70	71	31	74.6 ± 8.1	(58–90)	40	91.6 ± 8.6	(75–109)
Age ⩾70	46	26	75.6 ± 12.6	(51–100)	20	73.9 ± 10.6	(53–95)
	117	57			60		
Stage A	55	16	80.1 ± 13.3	(54–106)	39	91.9 ± 8.1	(76–108)
Stage B	19	12	89.9 ± 11.3	(68–112)	7	67.0 ± 11.4	(45–89)
Stage C	16	8	84.4 ± 8.8	(67–102)	8	79.7 ± 9.8	(60–99)
Stage D	31	23	49.7 ± 8.5	(33–66)	8	35.0 ± 13.0	(9–61)
	121	59		Stage D vs.* B,C	62		Stage D vs. A*
Gleason 2–4	26	6	84.7 ± 22.1	(41–128)	20	97.1 ± 11.9	(74–120)
Gleason 5–7	73	39	86.4 ± 8.3	(70–103)	34	86.4 ± 9.1	(69–104)
Gleason 8–10	19	13	25.4 ± 4.6	(16–34)	6	45.0 ± 15.4	(15–75)
	118	58		Gleason 8–10 vs. 2–4, 5–7*	60		
Diploid	58	25	83.4 ± 10.6	(63–104)	33	86.8 ± 8.8	(70–104)
Nondiploid	56	31	56.8 ± 6.5	(44–69)	25	88.2 ± 12.2	(64–112)
	114	56			58		

[a]SE, standard error.
*Significant, at $P < 0.05$.

TABLE IV. Summary of Prognostic Markers and Their Effects on Survival

Parameter (differences within)	Chi square	*P*
Stage (A,B,C,D)	16.375	<0.001*
Gleason score (2–4, 5–7, 8–10)	15.688	<0.001*
Age (<70 or ⩾70)	1.742	0.1869
Ki-67 (±expression)	1.451	0.2284
p53 (±expression)	0.628	0.4282
Ploidy (diploid vs. nondiploid)	0.055	0.8141

*Significant.

not expressing p53 and <70 years of age (93.8 ± 7.4). Similarly ploidy had no significant effect, although the shortest survival was found in those expressing p53 and having a nondiploid karyotype (54.4 ± 9.6).

Ki-67

Survivals (in months) for Ki-67 expression by variables are summarized in Table III. Overall, the mean survival SE for those expressing Ki-67 was 73.9 ± 7.0 (n = 59) and for those not expressing Ki-67 88.2 ± 6.9 (n = 62). Significant effects of Gleason grade ($P < 0.0001$) and stage ($P < 0.0001$) were noted based upon Cox regression analysis generating chi square analysis. This was best illustrated in those expressing Ki-67 and Gleason grades 8–10 having significantly ($P < 0.05$) diminished survivals (25.4 ± 4.6 months; 95% CL 16–34%) compared to those similarly expressing Ki-67, but having Gleason grades 2–4 (84.7 ± 22.1; 95% CL 41–128%), or Gleason grades 5–7 (86.4 ± 8.3; 95% CL 70–103%). Those expressing Ki-67 with stage D disease also had significantly ($P < 0.05$) diminished survivals (49.7 ± 8.5 months; 95% CL 33–66%) compared to those similarly expressing Ki-67 and having stage B (89.9 ± 11.3; 95% CL 68–112%) and stage C (84.4 ± 8.8; 95% CL 67–102%). In those not expressing Ki-67 those with stage D had significantly ($P < 0.05$) diminished survival (35.0 ± 13.0 months; 95% CL 9–61%) compared to those similarly lacking expression of Ki-67 with stage A disease (91.9 ± 8.1; 95% CL 76–108%). No significant effect on survival was noted when considering those <70 of age and those ⩾70, although the greatest survival 91.6 ± 8.6 months) was noted in those <70 and lacking Ki-67 expression. Similarly, no significant effect on survival was noted when considering normal diploid versus nondiploid karyotype, although the shortest survival (56.8 ± 6.5 months) was noted in those both expressing Ki-67 and having a nondiploid karyotype.

Analysis of Variance

The relation of variables is summarized in Table IV, where only differences between stage and Gleason score were significant by chi-square analysis.

DISCUSSION

Prognostic variables are important in prostate cancer management and allow the urologist to make appropriate therapeutic decisions. Many prognostic markers have

TABLE V. p53 Prognostic Ability in Prostate Cancer

Investigators	No. of patients	Predictive value	Comment
Thompson et al. [10]	29	Yes	Retrospective: 17% of prostate cancers were positive
Fox et al. [11]	45	No	13% of A-1 positive; no correlation with PSA or Gleason score
Hamdy et al. [12]	56	No	19.6% were p53 positive; expression did not correlate with PSA or Gleason score
Aprikian et al. [13]	93	No	14% were p53 positive; expression uncommon in low stage cancers
Thomas et al. [14]	68	Yes	13% expression. 40- vs. 76-mo survival for p53 positive tumors
Voeller et al. [15]	85	No	Only 3 of 8 prostate cancers expressed p53
Heidenberg et al. [16]	52	Yes	p53 expression 22% in 27 untreated and 80% of progressing disease
Kuczyk et al. [17]	76	Yes	p53 prognostic at 55-mo follow-up
Broder et al. [18]	71	Yes	p53 prognostic at 10.6-yr media follow-up
Curtis et al. [19]	63	Yes	p53 prognostic at 39-mo follow-up

TABLE VI. Ki-67 Prognostic Ability in Prostate Cancer

Investigators	No. of patients	Predictive value	Comment
Harper et al. [21]	86	Yes	Correlation with survival and grade, but not stage
Cher et al. [22]	44	Yes	Ki-67 index correlates with stage and grade
McLaughlin et al. [23]	45	No	Not predictive on follow-up
Westin et al. [24]	18	Yes	Castration resulted in short-term decrease in Ki-67 index
Veltri et al. [25]	124	Yes	At 8.6-yr follow-up, Ki-67 correlated with disease progression
Stattin et al. [26]	125	Yes	At 71-mo follow-up, expression correlated with survival
Coetzee et al. [27]	244	No	At 22–24 mo follow-up, only Gleason score and T stage predictive

been evaluated [6–8]. Two, p53 and Ki-67, have recently received increased attention and are the focus of this report.

p53 tumor suppressor gene is a nuclear phosphoprotein that arrests cells in G1 [9]. There have been several reports of its prognostic ability in prostate cancer [10–19] (Table V). In general, these reports suggest that prostate cancer expresses p53 less frequently than most other common human cancers. Moreover, it is seldom expressed in low-stage or low-grade tumors. An analysis of the results of the p53 expression in the 134 patients in this investigation suggested that, while increased expression correlated with a poorer survival, it did not significantly correlate with stage or Gleason score.

Ki-67 is a nuclear protein that is present in proliferating cells and can be measured by many antibodies [20]. There have been several reports of Ki-67 reactivity in prostate cancer [21–27] (Table VI). In general, these reports suggest that Ki-67 has prognostic capabilities. While the analysis of Ki-67 expression in the tumor tissue of the 121 patients in the investigation suggested that increased expression correlated with poorer survival, it did not reach statistical significance.

While both p53 and Ki-67 provided prognostic information it was statistically of less significance than either clinical stage or Gleason score. It is concluded that, while p53 and Ki-67 expression correlated inversely with survival, these expressions did not correlate with survival as strongly as did stage or Gleason grade.

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